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NON-HODGKIN'S LYMPHOMA AMONG ASTHMATICS EXPOSED TO PESTICIDES

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We conducted a pooled analysis of population-based case-control studies in Iowa, Minnesota and Nebraska to investigate whether asthma modifies risk of non-Hodgkin's lymphoma (NHL) associated with pesticide exposures. Cases (n = 872) diagnosed with NHL from 1980 to 1986 and frequency-matched controls (n = 2,381) randomly selected from the same geographic areas as the cases were included. Information on use of pesticides and history of asthma was based on interviews. Unconditional logistic regression was used to calculate ORs, adjusted for age, state and vital status. Of all subjects, 177 (45 cases, 132 controls) reported having been told by their doctor that they had asthma. Subjects with an asthma history had a nonsignificantly lower risk of NHL than nonasthmatics (OR = 0.6, 95% CI 0.3–1.4), and there was no main effect of pesticide exposure (OR = 1.0, 95% CI 0.8–1.2). However, asthmatics tended to have larger ORs associated with exposure to pesticides than nonasthmatics. The OR among asthmatics was 1.8 (95% CI 1.1–3.2) for ever-use of crop insecticides, 2.7 (95% CI 1.0–7.2) for chlordane, 2.4 (95% CI 1.0–5.7) for lindane and 3.7 (95% CI 1.3–10.9) for fonofos. Among nonasthmatics, ORs were 1.1 (0.9–1.3), 1.5 (1.1–2.2), 1.3 (0.97–1.8) and 1.6 (1.0–2.4), respectively. Although there is limited power for assessing interaction, our results suggest that the risk of NHL among asthmatics with pesticide exposure may be higher than among nonasthmatics with pesticide exposure.

Key words: *asthma; insecticide; farmer; non-Hodgkin's lymphoma; pesticide exposure*

Incidence and mortality rates for non-Hodgkin's lymphoma (NHL) have been increasing worldwide over the past several decades.[1] Although the reasons for this increase are not fully understood, NHL is known to be associated with a compromised immune system, particularly acquired or genetic immunodeficiencies.[2,3] Medical conditions related to more subtle immune alteration, such as asthma and other allergic conditions, have also been studied as potential risk factors for NHL.[4–10] These reports have described a decreased risk for NHL among persons with a history of asthma or allergies,[4,5] no association[6–8] or an increase in risk.[9,10] Exposure to pesticides has also been suggested as a possible risk factor for NHL.[11–15] Pesticides may increase cancer risk by altering the immune system.[16–19] Because both asthma and pesticide exposure may change the risk of NHL by immunologic alterations, we investigated the relation between pesticide exposure, asthma and risk of NHL.

MATERIAL AND METHODS

Study population

We pooled data from 2 population-based case-control studies of NHL in 3 midwestern states in the United States, which have been described in detail previously.[20,21] In Iowa and Minnesota, all newly diagnosed cases of NHL among white men aged ≥30 were ascertained from records of the Iowa State Health Registry and a special surveillance system of Minnesota hospitals and pathology laboratories from 1980 to 1983 (n = 530). In Nebraska, all cases of NHL diagnosed between July 1983 and June 1986 among white men and women aged ≥21 in 45 eastern counties were identified through the Nebraska Lymphoma Study Group and area hospitals (n = 346). All cases were reviewed by pathologists, and only histologically confirmed cases were included in this analysis. Controls were randomly selected from the same geographic areas as cases with frequency matching by race, gender, age (5-year age group) and vital status at the time of interview. Control/case matching ratios were approximately 2:1 in Iowa and Minnesota and 4:1 in Nebraska. For living cases under the age of 65, controls were selected by 2-stage random digit dialing.[22] For living cases aged 65 and over, controls were selected from the records of the Health Care Financing Administration. Controls for deceased cases were selected from death records in each state, with additional matching for year of death. Persons whose underlying cause of death was NHL, Hodgkin's lymphoma, multiple myeloma, leukemia or malignancy of unknown sites were excluded as controls. A total of 2,357 controls (Nebraska 1,318, Iowa and Minnesota 1,039) were identified.

Interview

Interviews were conducted with subjects or their next-of-kin if subjects were dead or incapacitated. Interviews were held in person in Iowa and Minnesota and by telephone in Nebraska. Participation rates among cases were 89% in Iowa and Minnesota and 91% in Nebraska. Among controls, rates were 78% in Iowa and Minnesota and 85% in Nebraska. We used standardized and structured questionnaires to collect information on use of pesticides and other known or suspected risk factors for NHL. Questions included personal handling of groups of pesticides and individual pesticides used on crops or animals, with year of first and last use. We also asked whether subjects had ever been told by a doctor that they had asthma and, if so, their age at first diagnosis.

Statistical analysis

Subjects who did not have any information on asthma (n = 25) were excluded from the pooled data set, leaving 872 cases and 2,336 controls eligible for analysis. We used unconditional logistic regression to obtain odds ratios (ORs) and 95% confidence intervals (CIs) with Stata software (version 7.0).[23] The ORs for NHL among farmers exposed to pesticides with asthma were compared to those of nonfarmers without asthma (*i.e.,* individuals who had never lived or worked on a farm and did not have asthma) and to those of farmers without asthma. We estimated the risk of NHL by reported use of individual pesticides where sufficient numbers of exposed subjects were available. We present ORs for pesticides

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that were personally handled by at least 5 exposed cases. The logistic model included age (<60, 60–75, >75), state (Iowa, Minnesota, Nebraska) and vital status (alive, dead). Other variables, such as gender, smoking, having a first-degree relative with lymphohematopoietic cancer, ever having a job correlated with lymphohematopoietic cancers (*e.g.,* painting or welding) and use of protective equipment, were also evaluated as possible confounders. Adjustments of ORs for these variables had minimal impact on risk estimates of NHL, and the latter 2 variables have some missing cases. These variables were not included in the final model. To assess possible reporting bias, risks were estimated including and excluding proxy respondents. We also explored the risk of NHL by age at first diagnosis of asthma and duration of pesticide use.

RESULTS

Table I shows the distribution of the 872 cases and 2,336 controls by asthma history, age, gender, vital status, state of residence, having a first-degree relative with lymphohematopoietic cancer and type of NHL. Of the total subjects, 177 (5.5%) reported having been told by their doctor that they had asthma. Asthmatic NHL cases were more likely than asthmatic controls to be younger, male, alive at the time of interview and residing in Iowa. Nonasthmatic NHL cases were more likely than nonasthmatic controls to be male, to have family history of lymphohematopoietic cancer and to reside in Iowa/Minnesota.

We evaluated ORs for NHL by pesticide groups and asthma history (Table II). Among nonfarmers, subjects with asthma had a lower risk for NHL (not statistically significant) compared to nonfarmers without asthma (OR = 0.6, 95% CI 0.3–1.4). ORs for NHL among farmers without asthma were near 1.0 for all pesticide categories except chemical classes of insecticide. The risk of NHL was significantly increased for exposure to crop insecticides (OR = 1.8, 95% CI 1.1–3.2) and nonsignificantly increased for exposure to livestock insecticides (OR = 1.4, 95% CI 0.9–2.3), herbicides (OR = 1.5, 95% CI 0.9–2.5) and fungicides (OR = 1.4, 95% CI 0.5–4.3) among farmers with asthma. Only organophosphate insecticides had significant ORs among both asthmatics and nonasthmatics. The pattern was consistent by state of residence or interview type, although the results were limited by small numbers of cases (data not shown).

Table III presents ORs for NHL among farmers exposed to individual pesticides by asthma history. Among insecticides, risk of NHL was significantly elevated with exposure to chlordane (OR = 2.7, 95% CI 1.0–7.2), fonofos (OR = 3.7, 95% CI 1.3–10.9) and lindane (OR = 2.4, 95% CI 1.0–5.7) in asthmatics compared to nonfarmers without asthma. Many other insecticides (aldrin, carbaryl, carbofuran, diazinon, dieldrin, flyspray, heptachlor, malathion) also had larger ORs among farmers with a history of asthma than among those without asthma. However, none of these was significantly different from the risks in nonasthmatics. Among nonasthmatics, risk of NHL was also significantly elevated with exposure to chlordane, diazinon, fonofos and malathion; but the magnitude of risk was smaller than that among asthmatics. Use of individual herbicides was also associated with increased risk of NHL among asthmatics compared to nonasthmatics, but only cyanazine had a significant OR. No fungicide had 5 or more exposed cases and was significantly associated with NHL.

Analyses of pesticide exposure and asthma history among farmers only are presented in Table IV. The reference category was nonasthmatic farmers not exposed to each pesticide. Asthmatics with exposure to crop insecticides had significantly elevated risk of NHL (OR = 2.0, 95% CI 1.1–3.5), but the interaction risk for pesticide exposure and asthma was not statistically significant.

We explored the potential modifying effects of age at first diagnosis of asthma and duration of pesticide use on risk of NHL (Table V). Only asthmatic farmers exposed to pesticides were included in this analysis. Risks among subjects diagnosed with asthma after age 30 tended to be higher for all types of pesticide than those among subjects who had developed asthma relatively early. There was no clear pattern of ORs for NHL by duration of pesticide use and age at diagnosis of asthma. The results were limited due to the small number of asthmatic NHL cases, and further studies are needed to investigate these findings.

DISCUSSION

We found that farmers with potential exposure to pesticides and a history of asthma tended to have higher relative risks for NHL than pesticide-exposed farmers not reporting asthma. The excess risks among asthmatics with pesticide exposure were generally more pronounced when we analyzed by individual pesticides (*e.g.,*

TABLE I – CHARACTERISTICS OF CASES AND CONTROLS BY ASTHMA HISTORY

Characteristics	Nonasthmatics (n = 3,031)		Asthmatics (n = 177)	
	Cases (n = 827)	Controls (n = 2,204)	Cases (n = 45)	Controls (n = 132)
Age (years)				
<60	231 (27.9)[2]	585 (26.5)	18 (40.0)	24 (18.2)
60–75	348 (42.1)	875 (39.7)	17 (37.8)	51 (38.6)
>75	248 (30.0)	744 (33.8)	10 (22.2)	57 (43.2)
Gender				
Male	676 (81.7)	1,594 (72.3)	38 (84.4)	100 (75.8)
Female	151 (18.3)	610 (27.7)	7 (15.6)	32 (24.2)
Vital status				
Alive	572 (69.2)	1,486 (67.4)	34 (75.6)	71 (53.8)
Dead	255 (30.8)	718 (32.6)	11 (24.4)	61 (46.2)
State of residence				
Iowa	238 (28.8)	483 (21.9)	15 (33.3)	26 (19.7)
Minnesota	264 (31.9)	491 (22.3)	10 (22.2)	28 (21.2)
Nebraska	325 (39.3)	1,230 (55.8)	20 (44.5)	78 (59.1)
Family history of cancer[1]				
No	733 (90.7)	2,072 (95.4)	42 (93.3)	120 (92.3)
Yes	75 (9.3)	99 (4.6)	3 (6.7)	10 (7.7)
Histologic type				
Follicular	243 (29.5)	—	18 (40.9)	—
Diffuse	298 (36.1)	—	16 (36.4)	—
Small lymphocytic	90 (10.9)	—	4 (9.1)	—
Other	194 (23.5)	—	6 (13.6)	—

[1]Lymphohematopoietic cancers diagnosed in any first-degree relative.–[2]Percentage in parentheses.

TABLE II – RISKS OF NHL BY FARMING HISTORY, PESTICIDE USE AND ASTHMA HISTORY

	Nonasthmatics				Asthmatics			
	Cases	Controls	OR[1]	95% CI	Cases	Controls	OR	95% CI
Nonfarmers	259	684	1.0	Ref[2]	9	37	0.6	0.3–1.4
Farmers	560	1,510	1.0	0.8–1.2	36	95	1.1	0.7–1.6
No pesticide use	137	419	1.0	0.8–1.3	3	14	0.7	0.2–2.6
Pesticide use	423	1,091	1.0	0.8–1.2	33	81	1.1	0.7–1.7
Animal insecticides	363	900	1.0	0.8–1.2	28	52	1.4	0.9–2.3
Crop insecticides	239	572	1.1	0.9–1.3	23	32	1.8	1.1–3.2
Organochlorine	205	412	1.2	0.9–1.5	17	28	1.5	0.8–2.8
Organophosphate	149	269	1.4	1.1–1.7	14	17	2.0	1.0–4.2
Carbamate	79	154	1.3	0.9–1.7	8	9	2.2	0.8–5.9
Herbicides	260	639	1.0	0.8–1.3	23	43	1.5	0.9–2.5
Phenoxyacetic acid	176	409	1.0	0.8–1.3	17	33	1.3	0.7–2.4
Triazine	131	268	1.1	0.9–1.5	12	17	1.7	0.8–3.7
Amides	105	231	1.1	0.8–1.4	11	15	1.8	0.8–3.9
Fungicides	44	110	1.0	0.7–1.4	5	10	1.4	0.5–4.3

[1]OR adjusted for age, vital status and state.–[2]Ref, reference category was nonfarmers without asthma (259 cases, 684 controls) for all ORs.

TABLE III – RISKS OF NHL AMONG FARMERS EXPOSED TO INDIVIDUAL PESTICIDES[1] BY ASTHMA HISTORY

	Nonasthmatics				Asthmatics			
	Cases	Controls	OR[2]	95% CI	Cases	Controls	OR	95% CI
Nonfarmers	259	684	1.0	Ref[3]	9	37	0.6	0.3–1.4
Insecticides								
Aldrin	66	148	1.0	0.7–1.5	10	11	2.1	0.9–5.1
Carbaryl	42	77	1.4	0.9–2.0	6	6	2.4	0.8–7.6
Carbofuran	56	117	1.2	0.8–1.7	6	8	1.9	0.7–5.6
Chlordane	67	108	1.5	1.1–2.2	9	8	2.7	1.0–7.2
DDT	158	313	1.2	0.9–1.5	11	24	1.2	0.6–2.4
Diazinon	58	98	1.6	1.1–2.3	7	9	1.9	0.7–5.3
Dieldrin	30	63	1.2	0.7–1.9	5	3	4.2	0.98–18.2
Flyspray	189	442	0.9	0.7–1.1	14	27	1.1	0.6–2.2
Fonofos	41	69	1.6	1.0–2.4	8	6	3.7	1.3–10.9
Heptachlor	44	84	1.3	0.9–2.0	6	6	2.6	0.8–8.4
Lindane	84	146	1.3	0.97–1.8	11	11	2.4	1.0–5.7
Malathion	89	141	1.5	1.1–2.1	7	9	1.9	0.7–5.1
Herbicides								
2,4-D	172	402	1.0	0.8–1.3	17	33	1.3	0.7–2.5
2,4,5,-T	36	77	1.1	0.7–1.8	7	8	2.2	0.8–6.1
Alachlor	96	210	1.1	0.8–1.4	10	14	1.7	0.8–4.0
Atrazine	119	225	1.3	0.96–1.6	9	16	1.4	0.6–3.3
Butylate	38	75	1.1	0.7–1.7	5	6	2.0	0.6–6.9
Chloroamben	52	103	1.1	0.8–1.6	9	10	2.3	0.9–5.7
Cyanazine	53	131	0.9	0.6–1.3	8	7	2.8	1.0–8.1
Dicamba	49	106	1.0	0.7–1.5	6	7	2.0	0.6–6.0
Glyphosate	53	91	1.4	0.98–2.1	6	12	1.2	0.4–3.3
Trifluralin	73	168	1.0	0.7–1.3	8	10	1.9	0.7–4.8

[1]At least 5 cases handled each individual pesticide were included in this analysis.–[2]OR adjusted for age, vital status and state.–[3]Ref, reference category was nonfarmers without asthma (259 cases, 684 controls) for all ORs.

chlordane, fonofos, lindane, cyanazine) and occurred when either "nonfarmers" or "farmers" was used as the reference.

Although we had limited power for assessing effect modification, there might be synergism between asthma and pesticide exposure for developing NHL. One possible explanation is that there is immune deviation in asthma toward T-helper 2 (Th2) predominance, with elevated IL-4, IL-5 and IL-13, which might inhibit Th1 responses that could protect against cancer.[24,25] This skewing of the immune response toward the Th2 phenotype could exacerbate the effects of the pesticides, which may partly act as carcinogens, and may also inhibit the immune response, acting synergistically with the asthma. Some pesticides might also inhibit a different arm of the immune response, *e.g.,* cytotoxic T lymphocytes or natural killer (NK) cells,[26,27] so that the combination of asthma and pesticides exposure eliminates more than one mechanism of immunosurveillance. Moreover, IL-13, which is prominent in asthma, can also downregulate cytotoxic T lymphocyte–mediated tumor immunosurveillance,[28] reducing 2 arms of the immune response to cancer and specifically crippling immunosurveillance against cancer in a murine tumor model.

Various characteristics, such as history of allergy and serum IgE levels, between late-onset and early-onset asthma[29–31] might be related to higher risk of NHL among individuals diagnosed with asthma over age 30. Exposure to pesticides may influence the induction and aggravation of asthma through modification of autonomic control of airways.[32] Associations between asthma and use of cholinesterase-inhibiting pesticides were observed among Canadian farmers[33] and U.S. pesticide applicators.[34]

The strengths of our pooled study are a population-based design, high response rates and detailed information on pesticide use and potential etiologic factors for NHL. The relatively large sample size facilitated the simultaneous evaluation of asthma and pesticide use but was still not enough to carefully evaluate individual pesticides and asthma in relation to NHL.

We used self-reported information concerning prior asthma history. The sensitivity of ascertainment of physician-diagnosed asthma has been estimated at about 68% and the specificity at about 94% when validated against clinical diagnosis.[35] This type of misclassification is likely to cause underestimation of the asso-

TABLE IV – RISKS OF NHL AMONG FARMERS BY PESTICIDE EXPOSURE AND ASTHMA HISTORY[1]

	Nonasthmatics			Asthmatics			Interaction OR (95% CI)
	Cases	OR[2]	95% CI	Cases	OR	95% CI	
Any pesticide							
No	137	1.0	Ref[3]	3	0.7	0.2–2.5	
Yes	423	1.0	0.8–1.2	33	1.1	0.7–1.7	1.6 (0.4–6.2)
Crop insecticides							
No	252	1.0	Ref	12	0.9	0.5–1.8	
Yes	239	1.2	0.9–1.4	23	2.0	1.1–3.5	1.9 (0.8–4.6)
Animal insecticides							
No	143	1.0	Ref	6	0.8	0.3–2.1	
Yes	363	1.0	0.8–1.3	28	1.4	0.9–2.4	1.7 (0.6–4.9)
Herbicides							
No	232	1.0	Ref	12	1.0	0.5–1.9	
Yes	260	1.1	0.9–1.4	23	1.6	0.9–2.8	1.4 (0.6–3.4)
Fungicides							
No	433	1.0	Ref	28	1.2	0.8–1.9	
Yes	44	1.0	0.7–1.5	5	1.5	0.5–4.5	1.2 (0.4–4.2)

[1]Nonfarmers were excluded from this analysis.–[2]OR, adjusted for age, vital status and state.–[3]Ref, reference category was nonasthmatic farmers not exposed to each pesticide.

TABLE V – RISKS OF NHL AMONG ASTHMATIC FARMERS BY AGE AT FIRST DIAGNOSIS OF ASTHMA AND DURATION OF PESTICIDE USE[1]

Age at first diagnosis (years)	Duration of pesticide use					
	≤50th percentile			>50th percentile		
	Cases	OR[2]	95% CI	Cases	OR	95% CI
Any pesticide						
≤30	3	1.0	Ref[3]	8	4.5	0.7–27.3
>30	6	16.3	1.7–156.8	6	5.0	0.7–37.1
Crop insecticides						
≤30	4	1.0	Ref	6	2.5	0.3–19.6
>30	3	2.3	0.2–31.1	4	14.1	0.8–257.7
Animal insecticides						
≤30	3	1.0	Ref	6	2.8	0.4–19.5
>30	4	15.1	0.95–240.2	8	5.0	0.7–37.8
Herbicides						
≤30	2	1.0	Ref	6	1.7	0.1–29.4
>30	4	3.2	0.1–99.5	4	2.3	0.1–51.3

[1]Only asthmatic farmers exposed to pesticides were included in this analysis.–[2]OR adjusted for age, vital status and state.–[3]Ref, reference category was asthmatic farmers in the category of ≤30 years of age at first diagnosis of asthma and ≤50th percentile of each pesticide use.

ciation between asthma history and NHL risk. However, we think misclassification *per se* is unlikely to explain the observed effect of asthma because the reported prevalence of asthma in our study (5.5%) was consistent with that reported in other populations, ranging from 5% in the Agricultural Health Study in the United States[34] to 4–6% in rural Saskatchewan in Canada.[33,36] Asthma prevalence was also similar by self (5%) and proxy (6%) respondents.

Although farmers provide considerably accurate detail regarding past pesticide use,[37–39] misclassification of exposure is a concern. Use of proxy respondents may introduce nondifferential misclassification bias;[40] however, responses from proxies are reported to be adequate for epidemiologic studies of pesticides and cancer.[41] Our analyses based on direct interviews found the same pattern of results as seen for proxy respondents (data not shown). Based on a study of the quality of information on pesticide use provided by farmers or their proxy respondents,[42] the degree of misclassification was generally in the range observed for other factors obtained by interview in epidemiologic studies of such factors as diet and use of tobacco and alcohol. Therefore, it appears unlikely that misclassification of exposure could explain the observed increase in the risk of NHL among asthmatics exposed to pesticides.

Differential reporting bias is also a concern in case-control studies and could have resulted from an increased likelihood of cases to remember pesticide exposures compared to controls. However, comparison of reporting by cases and controls regarding pesticide use among our subjects provided no evidence of differential response bias.[37]

In summary, our findings suggest that the risk of NHL among asthmatics with pesticide exposure may be higher than that among nonasthmatics with pesticide exposure. Considering the widespread use of pesticides and the relatively high prevalence of asthma, further studies, particularly with carefully defined asthma diagnosis and biomarkers, such as cytokine levels and activity of different T and NK cells, are needed to confirm these findings and clarify the mechanisms involved.

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